Discussion

Multiple Targeted Therapies: Is there a Place for Vach Type-3 or Type-4 Design Trials

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Summary

Invited comment on Vach W. and dePoint Christensen R. (2006). Making efficient use of patients in designing phase III trials investigating simultaneously a set of targeted therapies with different targets, *Biometrical Journal* **48**, 897–907.

For complexity reasons the designs proposed by Vach et al. will probably not be used in initial drug registration trials. But they may be an option for established study groups that run treatment-optimisation or indication-extension trials investigating targeted drugs that are already registered.

Key words: Study design; Targeted therapies.

1 A Landmark Paper

A wave of targeted anti-cancer therapies is under development and may revolutionise treatment strategies in oncology in the near future. Targeted therapies will lead to increasingly individualised treatments. They will create a problematic tendency to split up traditional study populations and thus new types of study designs may be required.

The landmark paper of Vach et al. has the merit to formally pose the resulting study design problems from a study group statistician's point of view. It lucidly sets out the paradigm for design considerations when dealing with multiple targeted drugs addressing partially overlapping subpopulations within a disease entity. And it proposes an appealing novel family of designs.

In planning a study involving multiple targeted drugs, study group biometricians now can and should investigate potential savings in patient numbers using one of the new designs. Given assumptions on the prevalence of the target conditions one can easily compute the resulting number of informative patients for a given treatment using the rules detailed in the paper. However, these savings should be carefully contrasted with the statistical, practical and "political" disadvantages caused by using a more complicated design.

2 Open Design Problems

Several statistical problems need to be further addressed:

Is multiplicity adjustment required? Type-2 designs may be seen as independent separate trials. Type-4 (J) designs may be seen as combining standard two arm trials and J-factor factorial design trials for which multiplicity adjustment may be argued to be unnecessary. But type-3 designs include a component of many treatments versus control for which multiplicity adjustment is standard. In this case test statistics for the contrasts are positively correlated to some extent and possibly design-specific methods of multiplicity adjustment may be needed.

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Thus possible gains in patient numbers may be attenuated by the requirement to power the study for multiplicity-adjusted significance levels. The alternative proposal to use a closed testing procedure runs the risk that a drug specific comparison turns out to be nominally significant, but cannot be claimed because the global test does not reject. This may be acceptable to a study group, but is difficult to swallow for a company involved.

As in usual factorial designs, the type-4 designs rely on the assumption that there are no relevant interactions between the treatments. If major interactions emerge the interpretation of the trial may become difficult. An assessment of robustness of the design concerning interactions may be indicated.

Other problems concern the conduct of the trial: If the prevalence of the conditions targeted are not roughly equal either over- or under-recruiting will occur or provisions for partially closing down the study with respect to high prevalence drugs have to be installed. A similarly open problem concerns a tailored interim analysis strategy.

3 Who Might Use a Vach Design-3 or Design-4 Trial Under what Circumstances?

"Keep it simple" is a major principle for study design. So the key question is: Type-3 or type-4 designs, recommendable for whom under what circumstances?

Vach et al. try to maximise information gain per patient at the cost of substantial complexities in trial design, data analysis and study management. The trade off between optimal use of patients and complication costs is difficult to quantify. But it is clear that additional study complexity can only pay off if study patients are rare, costly or difficult to recruit.

Global player pharmaceutical companies will tend to address common diseases first. They will avoid unnecessary co-operation and information-sharing with rival companies and are keen to obtain clear cut, easy to present trial data for drug registration. When target conditions overlap, companies will simply compete for patients admissible for both drugs addressing individual centres based on market principles, i.e. offering lucrative case money.

In addition, safety concerns (prior pilot trial for combinations?), ethical concerns (exposure of a patient to two unproven drugs?) and agency regulations (SAEs analysis with multiple novel study drugs?) make it very difficult to use type-4 designs in a drug registration context even if a single company had multiple drugs simultaneously ready for registration. Thus I predict that the novel designs will not be used for initial drug registration trials.

On the other hand, established well organised independent study groups – often organised within medical societies – have an important mission in optimising treatment strategies in oncology and organising high quality patient care. They typically have a long term record of successive treatment optimisation trials and a stable source of study patients recruited from dedicated centres. In best examples the trials run by the study group include a majority of all eligible patients with the given disease and constitute a de-facto standard treatment (a guideline) for a specific entity within the scope of the study group.

Such established study groups have a high interest to continue all-inclusive trials for the whole of their patient population. With their regional or national scope, patient numbers may be limited. Study groups may want to make optimal use of "their" recruitment potential to improve outcome in "their" patients and the group's scientific output. Although such study groups want and need targeted therapies for their patients they will try to avoid scattering their patients in disjoint industry driven trials. It is from the perspective of such an established study group that Vach et al. have addressed the problem of multiple targeted therapies.

Not only industry will run trials with targeted therapies. Disease focussed study groups will either want to investigate how to best integrate already registered targeted drugs into standard treatment or run trials with already registered targeted therapies in new indications. In these situations safety

data already exist, and regulatory constraints and competition between companies should be less important.

The designs proposed by Vach et al. thus may be an option for established study groups driven treatment-optimisation- or indication-extension-trials in not too common diseases investigating drugs that are already registered.

References

Vach, W. and dePoint, Christensen R. (2006). Making efficient use of patients in designing phase III trials investigating simultaneously a set of targeted therapies with different targets. *Biometrical Journal* **48**, 897–907.

